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Review

Rodent models of social stress and neuronal plasticity: Relevance to depressive-like disorders

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ABSTRACT

Exposure to severe or persistent social stress may lead to the development of psychiatric disorders such as anxiety and depression. These mood disorders are associated with structural alterations of neural architecture in limbic brain regions that control emotion, mood and cognition. Structural remodeling may either be a sign of successful adaptation, or of failure to do so. In neuropsychiatric disorders like depression structural remodeling involves apoptosis, reduced neurogenesis, and structural remodeling of neuronal dendrites which most likely reflects the latter. Here we review key findings from animal models of psychosocial stress that have been used to gain insights into the relation between stress-related behavioral disorders like depression and structural plasticity. Specifically, we focus on models having a high face validity like social defeat stress in the resident-intruder paradigm and chronic stress of social subordination in social housing conditions. Moderate to severe social stress appears to stimulate plasticity and neuronal growth in regions of the amygdala, whereas the effects in the hippocampus and prefrontal cortex tend to be opposite. A major focus of the current review is to characterize social stress induced structural changes in these brain regions, aiming to provide insight in pathways and factors that underlie behavioral effects of stress and depression.

1. Introduction

Depression is a severe psychiatric disorder which affects more than 3.5% of the world's population as reported by the World Health Organization (WHO). Stress has been considered a major risk factor in the development of mood and anxiety disorders, especially in individuals with certain genetic vulnerability [1,2]. Based on these findings, rodents exposed to high and sustained levels of stress have been used to study neurobiological mechanisms underlying mood and anxiety disorders in humans. These animal studies highlighted the critical role played by mechanisms involved in neuronal plasticity elicited by acute or chronic stress. Interestingly, stress-induced neuroplasticity was mainly observed in brain structures that are considered to be key in the behavioral symptoms of depression and may, therefore, provide convergence between human and rodent studies.

Brain imaging studies in patients have confirmed the findings in animal models and show selective structural changes across various limbic and non-limbic circuits in the brains of depressed patients [3–6]. These structural alterations range from total volumetric changes of specific brain areas that control emotion, mood and cognitive functions to changes at a cellular level [7–10]. Postmortem morphometric studies in brains from these patients revealed detailed alterations at a cellular level such as changes in neuronal densities, dendritic atrophy or hypertrophy, loss of neurons and glial cells in selected brain structures [11–13] supporting the idea that major depression may be related to impaired structural plasticity in some regions and increased plasticity in others.

Brain regions like the amygdala, hippocampus and medial prefrontal cortex (mPFC) are known to be directly involved in the regulation of the neuroendocrine and behavioral response to stress [14]. These responses are triggered as adaptive responses in the short-term (allostasis) but may become maladaptive in the long term (allostatic load). This particularly occurs when individuals are confronted with chronically stressful conditions that cannot be controlled or predicted [14,44]. Observations from neuroimaging studies in humans have clearly indicated that brain region specific functional and structural changes in patients with mood disorders [6,16–18] are similar to the brain changes observed following stress. The prefrontal cortex seems to

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have a decreased activity in severely depressed patients, which coincides with impaired decision-making and higher propensity to act on negative emotional valence resulting in suicidal behavior [19–21]. In addition, structural and functional abnormalities have also been found in depression in subcortical limbic brain regions like the hippocampus and amygdala. Decreased hippocampal volumes have been reported in depression, and patients with decreased hippocampal volumes are more prone to relapse [22–24]. Inconclusive results have been reported related to the changes in amygdalar volume. Some studies in depressive patients have shown reduced volume in the amygdala, but others show increased volume [24,25]. For instance, morphometric analysis with magnetic resonance imaging revealed that depressed women had a smaller amygdala core [9], while another study on both men and women reported a larger total amygdala volume in depressed subjects [26]. Furthermore, postmortem histopathological studies revealed reduced number of glial cells in the amygdala in major depressive disorder, while no change was found in neuronal numbers [27]. Studies suggest that the impairments in the structural plasticity and volumetric changes of these brain areas mentioned above contribute to the pathophysiology of mood disorders [3,28–30].

2. Responses to social stress in animals

The vast majority of information on the impact of stress on brain and behavior in animals has been gathered following exposure to non-social, physical stressors. In these cases, stressors mostly involve noxious or physically distressing stimuli such as electric foot shock, tail pinch, forced swimming, physical restraint or immobilization, water and food deprivation, cold exposure or soiled cages [31]. Most common stressors in humans, however, are psychosocial in nature. To bridge this gap between animal studies and humans, the focus is shifting to animal models with higher face validity, such as the social defeat stress paradigm in rodents and tupaia's (tree shrews). For example, the episodic social defeat in the resident-intruder paradigm is the situation where victim animals, usually males, are defeated by larger aggressive conspecific males and housed singly after one or more defeat experiences [32–34] (Fig. 1A). A variation to this resident-intruder paradigm is the so-called sensory contact model (Fig. 1B), where victims are housed in continuous close, visual and olfactory contact with neighboring attackers which makes this more a chronic social stress model with a dominant and a subordinate animal [35,36]. The third variant is also making use of hierarchical dominance contexts where chronic social stress of subordination is studied in hierarchical colony structures such as the visible burrow system [37–39] (Fig. 1C). A variety of studies have been performed in these social stress situations and their behavioral, physiological and neurobiological readouts indicate that these paradigms are useful to get a better understanding of how social stressors can lead to alterations in brain and behavior that are reminiscent of the pathologies observed in patients with mood and anxiety disorders.

Defeated animals in the resident-intruder paradigm and subordinate animals living in social colonies show profound changes in behavior [2,40]. Defeat produces specific behaviors resembling the signs and symptoms of humans with affective disorders, such as anhedonia, social avoidance, despair and anxiety. Furthermore, defeated animals reduce their locomotor activity and cease self-grooming behavior. Body weight is frequently reduced following the stress exposure and clear disturbances are observed in circadian patterns in body temperature and cardiac readouts like heart rate and blood pressure. Sleeping pattern is characterized by an increased number of early waking episodes [2,41,42].

Although there are many commonalities between social and non-social stressors like the rapid activation of the sympathoadrenal and the hypothalamic-pituitary-adrenal (HPA) axis [42,43], also some differences appear. Socially defeated, but not restrained, animals show activation of the medial hypothalamic responsive circuit, a region also engaged in different forms of social behavior [44]. Another difference between these stressors was reported in expression of c-*fos* in the amygdala brain regions. In a study using a 2-day stress paradigm containing restraint stress, increased *c-fos* expression was found in the basolateral and central nuclei of the amygdala [45]. With social defeat, on the other hand, higher levels of *c-fos* expression was observed in the medial nucleus of the amygdala [46]. Another study reported increased microglial activity in the medial amygdala following repeated social defeat stress, but not in chronic restraint stress [47,48]. Moreover, chronic restraint stress or long-term glucocorticoid treatment induces loss of hippocampal neurons [49] which failed to occur in male tree shrews after 4 weeks of psychosocial stress [41]. Hence, it seems that although physical and psychological stressors trigger a similar peripheral stress response there are notable differences in the neural activation of brain regions involved in the organization of this response.

This review will mainly focus on structural remodeling triggered by social stress in brain regions known to be affected in the development of mood disorders. We realize that animal stress models, including social defeat stress, not only induce behavioral and neurobiological changes mimicking human depression but also anxiety behavior. In this review, however, we will focus on translation toward depressive disorders. A comparison will be made with results obtained in non-social stress models.

3. Structural remodeling elicited by stress

Exposure to prolonged stress elicits divergent patterns of structural and functional changes in the hippocampus, amygdala and medial prefrontal cortex [50]. The most commonly studied neuro-morphological changes that contribute to volumetric changes of brain regions include alteration in dendritic arborization, including the number, shape and size of spines as well as neuronal and glial cell counts [29]. Early evidence of stress induced structural plasticity was established by a series of seminal studies by McEwen and colleagues that focused on the hippocampus. They observed significant apical dendritic atrophy occurring in the pyramidal neurons of the CA3 sub region of the hippocampus after 21 days of chronic restraint stress (CRS) [51–53]. Similarly, the prefrontal cortex showed dendritic atrophy in response to similar forms of stress [54–56]. In the amygdala, however, chronic immobilization stress has been shown to induce dendritic hypertrophy [57]. These variations in the structural effects across various brain regions could be due to cross-regional influences. Although these morphological changes are well established to occur after physical stressors such as restraint, the effects of psychosocial stress on the neuronal morphology remain largely unexplored. In particular, information on structural remodeling in the amygdala and mPFC following psychosocial stress exposure is relatively scarce.

3.1. Hippocampus

The hippocampus plays a pivotal role in cognitive functions and is a very sensitive and plastic brain region susceptible to stress. Structurally, the hippocampus consists of the dorsal hippocampus and the ventral hippocampus on the basis of various anatomical, behavioral and gene expression studies. The dorsal hippocampus, along with various cortical regions, is known for its involvement in cognitive functioning whereas the ventral hippocampus, along with the hypothalamus and the amygdala, is strongly related to the regulation of stress and emotions [58,59]. Since dorsal and ventral hippocampus differ not only in their respective functionality but also in their connectivity [59], stress may differentially affect these two regions [60]. This is also indicated in a study on rats that were subjected to 4 weeks of chronic unpredictable stress where a differential effect on dendritic remodeling across the dorso-ventral axis was shown. Volumetric reduction was observed in the dorsal hippocampus as a result of atrophy of CA3 and CA1 apical dendrites whereas increased ventral hippocampal volume was observed with hypertrophy in the CA3 apical dendrites [61]. Dendritic atrophy in

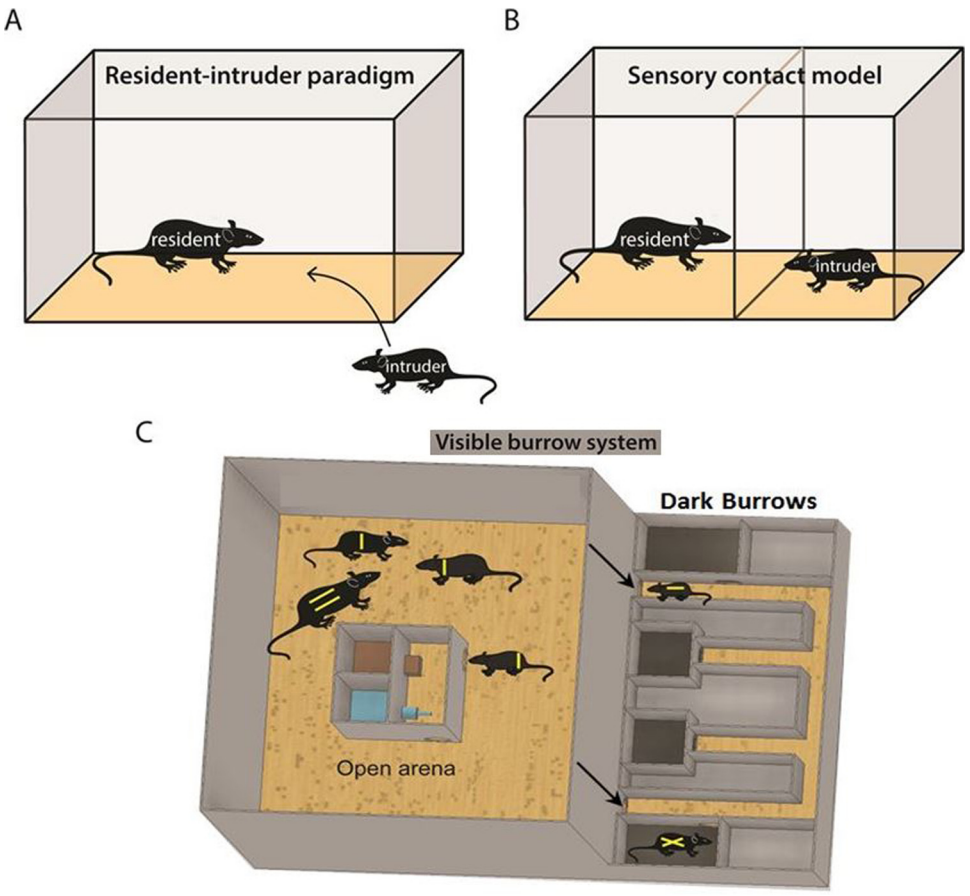

Fig. 1. Commonly used ethologically relevant animal models of social stress. (A) Social defeat stress models like resident-intruder paradigm, involving physical fight among animals followed by single housing of defeated intruder rats; and sensory contact model (B), where animals are housed in a compartment of the cage of the resident. At unpredictably moments a partition separating the two compartments is briefly removed allowing a physical conflict and defeat exposure. After replacement of the separator experimental animals experience continuous threat of defeat by visual and olfactory contact. (C) Schematic representation of the visible burrow system as currently used in our laboratory. In this semi-natural social structure there is an open arena with a circadian light-dark regime which is connected via two entry points (black arrows) with continuously dark burrows with tunnels and chambers. Behavior of animals in the burrows can be observed with an infrared camera because the burrows are covered with a fully black Perspex plate (Perspex 962 IR) that is only transparent for infrared light. Rats or mice can be individually recognized by fur-marking or fully automated tracking software. Social colony housing usually consists of single or mixed sex rodents housed together in a semi-natural environment. This leads to establishment of social hierarchy among animals which may induce stress in subordinates as well as in dominant animals.

the dorsal hippocampus was extensively shown in rodent exposed to non-social stressors [52,62]. Multiple factors may be causal in volumetric changes such as structural remodeling, neuro- and gliogenesis and apoptosis [29,63,64]. Social stress paradigms such as psychosocial stress in the resident-intruder paradigm and chronic stress of subordination in the visible burrow system in several animal models showed dendritic atrophy in CA1 and CA3 pyramidal neurons that persisted even after prolonged stress free recovery periods [39,41,65,66]. Somewhat surprisingly, dendritic atrophy in CA3 neurons was not only observed in animals exposed to chronic social stress but also observed in rats that were socially dominant in social colony structures like the visible burrow system [65] which may indicate that maintaining social dominance can be a source of chronic social stress. Rats that were exposed to repeated defeat exposure in the resident-intruder model [12] every other day for a period of 21 days showed strong reduction of the CA3 apical dendritic tree [67]. In the same study rats were exposed to a double defeat and sacrificed three weeks later. These animals not only showed a reduced apical tree of CA3 neurons but also a striking extension of dendrites of the basal tree of these neurons. This indicates that temporal dynamics may play an important role in dendritic remodeling of basal and apical trees and that this may relate to functional properties of the neurons involved [67]. Long-term psychosocial stress not only induces neuronal plasticity but also astroglial plasticity. Five weeks of psychosocial stress in adult male tree shrews decreased both the number and somal volume of astroglia which was significantly correlated with stress-induced hippocampal volume reduction [68].

Chronic stress not only causes dendritic remodeling but also changes spine shape and density depending upon duration, intensity and type of stressor. Evidence from various physical stressors has mainly reported decrease in spine density in CA3 and CA1 pyramidal neurons, associating it with depression like behaviors observed in the animals [69–71]. However, there are only few studies available which show alterations in the dendritic spines induced by social stress. Chronic social defeat stress in susceptible mice decreases dendritic spine density in the neurons of CA3 and dentate gyrus region of hippocampus [72]. Repeatedly defeated rats from a feral strain (wild-type Groningen rats) exhibited robust decrease in spine density in the CA1 pyramidal apical dendrites [66]. Another study showed a significant decrease in stubby spines, and an increase in long-thin spines within the CA1 stratum radiatum region when adolescent male mice were subjected to 10 days of defeat [73]. These structural brain changes are analogous to changes seen in a human postmortem study where the subjects had undergone severe psychological distress [74].

Neurons that are generated during adulthood represent a unique form of structural plasticity that can be regulated by the environment. It has been suggested that high levels of corticosteroids, as well as stressful conditions, may be correlated with accelerated damage resulting even in the loss of hippocampal pyramidal neurons [49]. Aversive social experiences have also been demonstrated to decrease the production of immature granule cells and also inhibit proliferation of granule cell precursors [75]. This can be due to reduction in gene expression in hippocampus important for neuronal proliferation and plasticity [76]. Exposure to paradigms of social subordination result in a decrease in neurogenesis in marmosets [77], tree shrews [34,63,78], and rats [79]. A suppressive effect of stress on the number of BrdU-labeled cells has been observed in the dentate gyrus of adult rats living as subordinates in a visible burrow system for 4 days [75]. A study in marmosets, however, showed no long-term consequence on neurogenesis when evaluated 2 weeks after psychosocial stress [80]. Neural plasticity and stress coping is also studied in teleost fishes where chronic social stress experienced by subordinate fishes in social hierarchies leads to suppression of brain cell proliferation [81].

3.2. Amygdala

Neurobiological studies have implicated the amygdala as one of the crucial brain areas in stress responses and the debilitating affective symptoms seen in stress-related psychiatric disorders, such as depression and chronic anxiety. Structurally, the amygdala is a complex brain region that is divided into three sub-nuclei: the basolateral nucleus (BLA), the corticomedial nucleus (MeA) and the central (CeA) nucleus [82] and these different nuclei play distinguishing roles in the regulation of fear and anxiety related behaviors [83,84]. Further, the BLA consists of lateral, basal and accessory basal nuclei of the amygdala. The BLA is essential for the formation and retrieval of conditioned fear memories [85] whereas, the CeA is an output nucleus of the amygdala [86]. The MeA is another major output nucleus of the amygdala which plays an important role in controlling social behaviors like sexual behavior, as well as the processing of predator odor-induced defensive reactions [87–89].

Animal studies have reported contrasting patterns of structural plasticity in the basolateral amygdala compared to the hippocampus and mPFC. Repeated social stress in rats induces enhanced dendritic arborization in the basal dendrites of BLA pyramidal neurons. This effect is accompanied by an increase in social avoidance behavior suggesting stress-induced increase in social anxiety in the rats [66]. This confirms the previously published effect using models of physical stressors such as restraint and immobilization [50,69]. Twenty-four hours after chronic immobilization stress, principal neurons in the BLA exhibit dendritic hypertrophy which persists even after three weeks of stress free recovery [57,90]. Further, similar to the BLA, enhanced dendritic arborization was also observed in the BNST but not in the CeA [91]. Interestingly, with chronic unpredictable stress, atrophy was observed in the bipolar but not in the principal neurons of the BLA. The animals subjected to chronic unpredictable stress also did not exhibit high anxiety-like behavior like those subjected to chronic immobilization stress when tested on the elevated plus-maze [57].

Chronic and acute immobilization stress are both known to enhance spinogenesis across both primary and secondary branches of spiny neurons in the BLA where acute immobilization stress induces gradual formation of new spines over time but without any effect on dendritic arbors [92]. Interestingly, this delayed generation of spines after acute immobilization stress was accompanied by a gradual development of anxiety-like behavior in rodents. This study shows that high anxiety in rodents can arise due to BLA spinogenesis in the absence of dendritic hypertrophy. Contrastingly, chronic immobilization stress has an opposite effect in the MeA where a loss of spines is observed which is suggested to be mediated by the extracellular matrix protease, tissue plasminogen activator, that has no role in spinogenesis in the BLA [93,94]. Social instability stress of 5 weeks exerted opposite effects on adolescent rats and adult rats, where adolescent rats reduced their dendritic field and spine density in basal and lateral amygdala neurons whereas adult rats showed increase in spine density. This study suggested that social instability stress hinders neuronal development in the amygdala in the adolescent brain, while mature neurons in the amygdala are capable of adapting to this type of stress [95]. Another subcortical limbic structure that is involved in mood regulation but also in reward mechanisms, the nucleus accumbens, shows increase in stubby spine density after 10 days of social defeat stress [96].

3.3. Medial prefrontal cortex (mPFC)

The medial prefrontal cortex is another region known to critically participate in regulating the behavioral and endocrine response to stress and is also affected by stress. It plays a key role in working memory, decision making and mediating higher executive functions. Broadly, the mPFC is composed of the prelimbic (PL) and infra limbic cortices (IL), each with distinct functions and interestingly opposite roles in conditioned fear expression and extinction [97,98]. Inactivation studies targeting the individual sub regions of the mPFC reveal that the PL cortex is required for fear expression while the IL cortex is required for fear extinction [99].

The neurons of the mPFC region are highly sensitive to stress and show structural plasticity in the same direction as hippocampal neurons. Five weeks of daily social stress is known to inhibit glial cell proliferation in the adult medial prefrontal cortex. In the same study, fluoxetine treatment has shown to counteract the inhibitory effect of stress [100]. The pyramidal neurons of mainly the prelimbic region undergo reversible structural remodeling like hippocampus [55,56,101,102]. On the other hand, dendritic atrophy in adult rats was not seen with repeated social defeat stress [66]. Moreover, with chronic restraint stress, an increase in the length and dendritic branching of the IL and PL pyramidal neurons was observed in females while opposite effects were observed in the male rats [103–105]. This sex difference in the structural remodeling following stress exposure was not only observed in the prefrontal cortex but also in the hippocampal CA3 neurons where female rats did not show apical dendritic atrophy after restraint stress [106]. An explanation for the sexual dimorphism is not yet available although differences in the glucocorticoid stress response and glutamatergic innervation of hippocampal regions are suggested to play a role [106].

Along with dendritic atrophy, spine loss is also observed in apical dendrites of the pyramidal mPFC neurons in male rats subjected to chronic restraint stress [55,56,107–109]. Interestingly, a partial reversibility of reduced spine density was shown after 21 days of stress free recovery [110]. Chronic restraint stress also alters spine morphology for instance, a reduction in mature mushroom spine density and increase in immature thin spine density was observed in male rats with an overall decrease in mean dendritic spine volume and surface area [111]. This shift in spine shape correlates with its functionality. Spine strength depends mainly on the density of incorporated glutamatergic receptors which are abundant in mature mushroom spines. Whereas, thin spines are functionally weaker [112]. These structural alterations are in line with human postmortem study where decreased expression of synapse-related genes responsible for loss of dendrites and spines was observed in subjects with major depression disorders [113].

Mechanisms underlying the structural alterations in these brain areas are currently explored extensively and a number are addressed in the section below. However, our understanding of these mechanisms is far from complete and hence, therapeutic intervention specifically targeting structural remodeling is not yet available. A basic understanding of the relation between these mechanisms involved in cellular and structural plasticity and depression can serve as the much needed push for neuroplasticity targeting therapeutics.

4. Mechanisms underlying structural plasticity

The mechanisms underlying structural remodeling in the brain areas discussed above are likely to be mediated by stress-induced changes in glucocorticoids, neurotrophic factors, neurotransmitters, genetics and epigenetic factors [69,114] (Fig. 2).

4.1. HPA axis and glucocorticoids

Mounting evidence has helped to understand the (mal)adaptive role of glucocorticoids in mediating the stress response in these brain areas [114]. In humans, HPA axis dysfunction is a consistent finding in depressed adults [115]. The levels of glucocorticoid hormones, being principal effectors in the stress response, rise from the activation of hypothalamic-pituitary-adrenal (HPA) axis induced by stress. Due to their lipophilic nature, these glucocorticoids directly impact the brain exerting a broad range of molecular, structural and functional effects through mineralocorticoid receptors (MR) and glucocorticoid receptors (GR) [116,117]. Stress alters expression of GR and MR mainly by downregulating them, as observed in the hippocampus, PFC and the

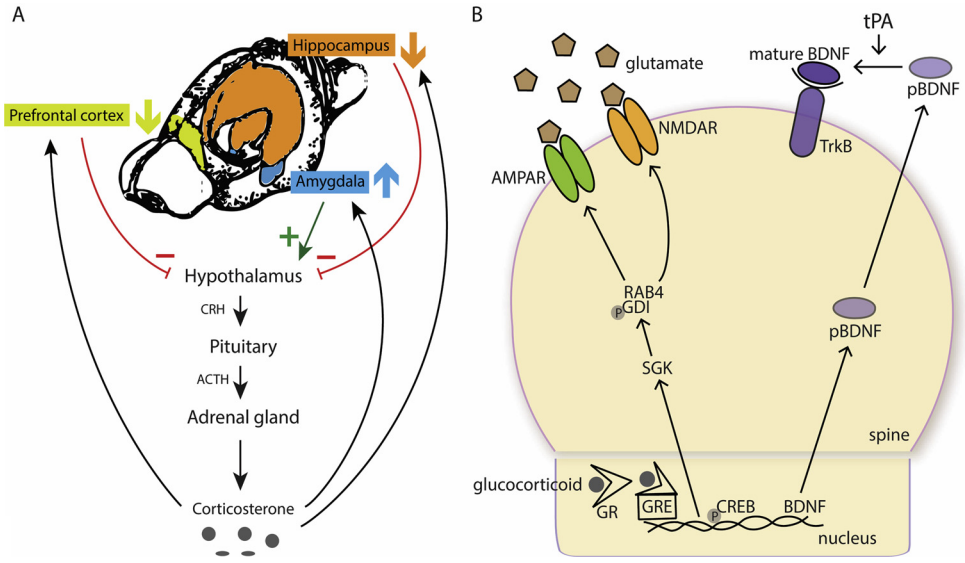

Fig. 2. (A) Brain areas involved in mediating a stress response by differentially activating the hypothalamic-pituitary-adrenal (HPA) axis include hippocampus, amygdala and prefrontal cortex. The hypothalamus secretes corticotropin-releasing hormone (CRH) in response to stress exposure. CRH in turn binds to specific receptors on pituitary cells, which produce adrenocorticotropic hormone (ACTH). ACTH is then transported via the blood circulation to the adrenal glands where it triggers the production and secretion of corticosteroids. Corticosterone subsequently negatively feeds back to activity of the HPA-axis via the hypothalamus, pituitary, hippocampus and prefrontal cortex while there is a positive feedback on HPA-activity via the amygdala. (B) Molecular players involved in stress-induced structural plasticity. Abbreviations: AMPAR – α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor, NMDAR – N-methyl-D-aspartate receptor, TrkB – tropomyosin receptor kinase B, BDNF – brain-derived neurotrophic factor, pBDNF – precursor BDNF, tPA – tissue plasminogen activator, GR – glucocorticoid receptor, GRE – glucocorticoid response element, SGK – serum and glucocorticoid-inducible kinase, GDI – GDP (guanosine diphosphate) dissociation inhibitor, p – phosphorylated, CREB – cAMP response element-binding protein.

amygdala [118–120], the regions which are known to regulate HPA axis differentially (Fig. 2A). If glucocorticoids and GR/MR expression would be directly linked to neuronal morphology and associated behavioral functionality, it is somewhat surprising that GR and MR are reported to be similarly suppressed in all these three regions. Particularly considering the fact that structural remodeling in hippocampal and prefrontal brain regions is frequently reported to be opposite to that in the amygdala. Subordinate rats exposed to social stress show decrease in expression of GR, MR, and growth-associated protein GAP-43 mRNAs in CA1 region of the hippocampus. This change in gene expression correlates with a rise in corticosteroid hormone level [37].

Findings from a study in male mice show that corticotropin-releasing hormone (CRH) and forebrain CRH receptor 1 (CRHR1) mediate some of the rapid effects of chronic social defeat stress on dendritic spine morphology and modulate learning and memory. The impaired spatial memory and CA3 neuronal dendritic remodeling induced by stress is prevented by forebrain CRHR1 deficiency in adult male mice. In addition, hippocampal expression of nectin-3, a synaptic cell adhesion molecule important in synaptic remodeling, was negatively affected by chronic stress in a CRHR1-dependent fashion. This reveals the importance of CRH-CRHR1 signaling in modulating social stress-induced cognitive, structural and molecular adaptations [121].

4.2. Neurotransmitters

Evidence from studies indicate that NMDARs (N-methyl-D-aspartate receptor) and glutamate are involved in stress induced structural remodeling in hippocampus, and PFC brain regions [114,122]. Glucocorticoids have been shown to act synergistically with neurochemical transmission, like glutamate, to regulate structural changes in the neurons [123]. The concentration of glutamate, which is the main excitatory neurotransmitter in the brain, along with expression of glutamate receptors, mainly NMDA and α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA), is altered in the brain by stress. This alteration could be due to glutamate receptor trafficking and mobility [123]. Acute stress increases extracellular glutamate levels and causes increased surface expression of NMDARs and AMPARs at the postsynaptic membranes as well as a substantial rise in the densities of these receptor clusters [123–125]. One of the signaling cascades which is activated by stress and glucocorticoid in the PFC region is through GR mediated activation of the serum- and glucocorticoid-inducible kinases (SGKs), which plays a role in controlling glutamate receptor trafficking through formation of GDI (GDP dissociation inhibitor)-RAB4 complexes [126]. However, in the hippocampus, excitatory amino acids released by the mossy fiber pathway plays an important role in the remodeling of CA3 neurons [120].

Chronic stress also leads to reduced number or weakened activity of the astrocytes [127]. This may lead to an increase in extracellular glutamate concentration in the synaptic cleft, eventually increasing the risk of excitotoxicity and cell damage. Another possible mechanism by which the altered activity of astrocytes can induce structural abnormalities is by decreased production of the neurotrophic factors. Astrocytes synthesize and release many neurotrophic factors such as brain-derived neurotrophic factor (BDNF), glial-derived neurotrophic factor and many more, which are vital for the neuronal health [128,129]. These neurotrophic factors regulate neuronal growth, maintenance, and plasticity, and their reduced availability can result in increased cellular vulnerability or even cell death [68].

4.3. Neurotrophic factors

Neurotrophic factors are neuromodulatory molecules that may mediate stress induced structural changes. BDNF, along with its receptor, tyrosine kinase receptor B (TrkB) and its downstream signaling pathway have been implicated in structural remodeling. Activation of its downstream effectors like Rho GTPases and cofilin leads to modulation of actin dynamics which is essential for spine growth and enlargement [130–132].

Chronic immobilization stress is known to elicit hippocampal dendritic atrophy in connection with reduced levels of BDNF whereas in the amygdala BDNF level increases, which in turn relates to dendritic hypertrophy in rodents [133–135]. Studies have also shown that transgenic overexpression of BDNF in mice has antidepressant effects and prevents hippocampal atrophy induced by chronic stress while at the same time causing spinogenesis in the BLA [136]. This would suggest that hippocampal atrophy is leading in the depressed mood. A study in mice shows, however, a general decrease in BDNF mRNA expression in hippocampus, amygdala as well as other subcortical and cortical brain regions 24 h after social defeat stress [137]. This is in contradiction to the increase in BDNF mRNA expression found in nucleus accumbens post defeat experience in rats [138]. Along with these findings, work from McAllister et al. [131] reveals a role of BDNF as a modulator of

Table 1
Comparison of non-social and social stress-induced spatiotemporal patterns of plasticity at different levels of neural organization. There are more similarities than dissimilarities observed comparing both types of stressors.

Different levels of neural organization	Hippocampus		Amygdala		mPFC	
	Non-social	Social	Non-social	Social	Non-social	Social
Behavior	Spatial memory contextual fear memory ↓ [50,151]	Contextual fear memory ↓ [152]	Fear memory anxiety ↑ [50]	Fear memory anxiety ↑ [15,153]	Working memory fear extinction ↓ [50]	Working memory fear extinction ↓ [152,154]
Neurons (dendrites)	↓ [50]	↓ [66]	↑ [50]	↑ [66]	↓ [50]	↔ [66]
Synapses (spines)	↓ [50]	↓ [66,72]	↑ [50]	↔ [66]	↓ [50]	↓ [72]
Molecules (BDNF)	↓ [50]	↓ [155]	↑ [50]	↑ [155]	↓ [156]	?

structural plasticity. Interestingly, evidence suggests a diagnostic potential of mature BDNF (mBDNF) and its precursor proBDNF in plasma to distinguish bipolar depression from major depressive disorders during acute depressive episodes. In the patients with major depressive disorders, ratio of mBDNF to proBDNF was significantly higher than those with bipolar depression [139]. A key regulatory element which plays an important role in the conversion of proBDNF to mBDNF is tissue plasminogen activator (tPA) [140]. In CA1 region of hippocampus and medial amygdala region, chronic stress induced loss of spines is mediated by tPA [70,94]. A recent study, however, indicates that the antidepressant action induced by ketamine may be caused by increasing the expression of tPA resulting in increased levels of mature BDNF at the cost of levels of proBDNF in the hippocampus of rats exposed to chronic unpredictable mild stress [141] (Fig. 2B).

Many other mechanisms involving signaling pathways and synaptic or cytoskeletal proteins are currently explored next to the processes mentioned above in their relationship to structural remodeling and behavioral changes including behavioral stress pathologies.

5. Conclusion

Despite the current interest in the use of social stress paradigms in animals to understand neurobiological consequences and etiology of depression and anxiety-related pathologies, there are also some limitations of using these models which should be taken into consideration. According to WHO records, women are more affected by depression than men. However, most of the studies in rodents measuring consequences of social stress make use of offensive aggression of males directed to competitor males in a territorial context. This offensive aggression of male residents or dominant males in a colony is, however, directed much less toward female conspecifics, which makes this model less attractive to study consequences of stress in females. Females do exhibit aggressive behavior and establish territories but tend to defend them less fiercely with agonistic behavior like males do [142]. Studies in hamsters and rats show that females do display male-like territorial behavior toward both male and female intruders [143–145]. This maternal aggression against intruders is expressed by females shortly before gestation till the first week postpartum and then gradually declines [146]. Up till now, however, it is not known whether these female aggressive attacks result in detrimental consequences modeling depressive-like behavioral disorders in either male or female victims. Frequent male intruder placement during lactation not only enhances maternal aggressive behavior but also has negative consequences for the growth of both mother and offspring [147]. In this respect this model can be considered as a chronic social stress model and can be used to study structural remodeling in the brain regions of socially stressed female rodents.

Another issue lies in the use of relatively docile laboratory rat strains. Stress in victimized animals is elicited best using highly aggressive conspecific resident or dominant males. Particularly in rats the propensity to show high levels of aggressive behavior decreased dramatically in the majority of laboratory strains with the process of domestication [148]. Rats from Long–Evans strains [38] and feral rats [148] do show this propensity and are therefore used frequently in rat models of social stress. An advantage of social stress models can be that ferocity and number of physical attacks and threats from residents/dominants are variable depending upon individual characteristics of these animals in defending their environment at a particular time. This may lead to unpredictable situations for intruder/subordinate animals and can further contribute to the behavioral and neurobiological responses to stress in animals since lack of predictability and controllability are crucial players in failing adaptive capacity [43]. Non-social stress models have the risk of habituation to the stressor because of their predictive nature.

Comparing stress-induced effects on neuronal plasticity between physical, non-social stressors such as restraint and social stressors reveals more similarities than dissimilarities at different levels of neural organization (Table 1). This supports the conclusions of Motta and Canteras [44], who compared neuronal activation following restraint and defeat stress. Differences are mainly observed in brain regions that are particularly involved in the control of social behavior like hypothalamic regions and the medial amygdala.

Also within the same stress model, being either social or non-social, differential effects on neuronal plasticity in brain regions are reported. Differences may occur due to environmental conditions (intensity, frequency and duration of the stressor, housing condition, previous experience, etc.) and endogenous factors (sex, age, strain, coping style, genetic make-up). An important factor to consider is how stress is perceived by the individual. Some individuals are rather resilient to the negative consequences of severe exposure to stress whereas other are susceptible. This may also be related to individual differences in coping styles. Trait-like differences in the behavioral and physiological response to environmental challenges are observed in animals with either a proactive (aggressive) or a reactive (docile) coping style [149]. Depending on the environmental conditions, negative health conditions may arise when there is a mismatch between the expressed coping style and the optimal behavioral response to successfully cope with an environmental stressor. In some situations, individuals having a high behavioral flexibility as observed in a reactive coping style may have a higher capacity to successfully adapt whereas in other situations proactive individuals being less sensitive to changes in their environment and responding in a more rigid and routine-like manner to environmental challenges may be more successful in coping with the situation [149,150]. Susceptible individuals are the ones which are more prone to develop psychiatric disorders like depression. Understanding functional differences in neural circuitry involved in coping with stress like prefrontal cortex and the amygdala will contribute to a better insight in unraveling the relevance of stress-induced structural plasticity in these brain regions in relation to differences in stress-resilience and susceptibility.

Depression is a very complex disorder. It is not possible to cover all the symptoms shown by human patients in rodent models focusing only on social stress paradigms. Therefore, using different stress paradigms to induce depressive-like symptoms can help to reproduce multiple

aspects of behavioral manifestations of the depressive syndrome. Connecting these alterations to processes involved in structural remodeling in specific brain regions will contribute to a better understanding of the pathogenesis of mood disorders and hopefully also to better treatment.

Competing interests

The authors declare no conflict of interest.

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